Congenital Malaria in a Nonidentical Twin

A. BENIGNO N. BALATBAT, MD
GEORGE W. JORDAN, MD
CRYSTIE HALSTED, MD
Sacramento, California

MALARIA REMAINS the leading cause of parasitic death in the world, causing 200 to 300 million cases of infection annually. In Africa alone, more than a million persons die of malaria each year; most are children. In the United States, more than 1,000 cases are reported annually, almost exclusively from travelers and immigrants from endemic areas; however, mosquito transmission has been reported in California, most recently in 1990.[1]

In contrast, congenital malaria remains relatively rare with only about 300 cases reported worldwide, although this may represent underreporting. In the United States, 49 cases have been reported since 1950.[2] The occurrence of congenital malaria in twins is even rarer with only 5 previous reports in the world literature.[3-7] We report a case of congenital malaria in the second of nonidentical twins.

Report of a Case

The patient, a 1-month-old Asian-Indian girl, was admitted to the University of California, Davis, Medical Center because for a week she had had fever, pallor, lethargy, and poor oral intake. She was born at another hospital prematurely by cesarean section at 33 weeks' gestation. She was the second of nonidentical twins. Both twins had uneventful perinatal courses and were discharged from the hospital after 11 days.

A week before admission, the patient was noted to be eating less and was vomiting her formula. The formula was changed, but there was no notable improvement when she was seen in follow-up three days later. By this time she was noted to be pale and to have tachycardia for which she was admitted with an impression of neonatal sepsis. A regimen of cefotaxime sodium and ampicillin was started. Her leukocyte count was 9.8×10^9 per liter (9,800 per mm^3), her hemoglobin level was 68 grams per liter (6.8 grams per dl), a hematocrit was 0.18 (18%), and the platelet count was 646×10^9 per liter (646,000 per mm^3). After one day, she was transferred to the University of California, Davis, Medical Center for further management when *Plasmodium vivax* was noted on the peripheral blood smear.

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From the Division of Infectious and Immunologic Diseases, Departments of Medicine and Pediatrics, University of California, Davis, School of Medicine, Sacramento.

Reprint requests to George W. Jordan, MD, University of California, Davis, Medical Center, Division of Infectious Diseases, Research Facility, 4815 Second Ave, Sacramento, CA 95817.

On initial evaluation, the neonate was pale, irritable, weighed 2.46 kg (5.4 lb), and had a temperature of 36.7°C (98°F), a heart rate of 148 beats per minute, and a respiratory rate of 56 per minute. Her sclerae were icteric, and the skin was jaundiced. Her abdomen was full but soft, the liver was palpable 2 cm below the right costal margin, and the spleen was palpable 2 cm below the left costal margin. The findings of the rest of the examination were unremarkable.

Laboratory tests revealed a leukocyte count of 5.8×10^9 per liter (5,800 per mm^3), a hemoglobin level of 54 grams per liter (5.4 grams per dl), a hematocrit of 0.148 (14.8%) and a platelet count of 43×10^9 per liter (43,000 per mm^3). The peripheral blood smear again showed a few intraerythrocytic forms of *P vivax*. Her bilirubin level was 54 μmol per liter (3.2 mg per dl); alkaline phosphatase, 177 units per liter; aspartate aminotransferase, 43 units per liter; and γ-glutamyl transferase, 180 units per liter. The Coombs' test was negative.

She was treated with a regimen of chloroquine phosphate with a loading dose of 10 mg base per kg, followed by three doses of 5 mg per kg given at 6, 24, and 48 hours after the initial dose. She was transfused 35 ml of packed erythrocytes. She responded well, and a repeat blood smear showed no parasites. She was discharged after six days.

The patient's mother was a 21-year-old Indian woman who had moved to the United States 11 months before from Punjab, India. She does not have a history of malaria. During the first trimester of her pregnancy, she had had fever for two weeks, which was treated with an unspecified antibiotic. The rest of the course of her pregnancy was uneventful.

She lived in Yuba City with her husband, three children, and other relatives, none of whom had had malaria. Mosquitos are present in this locality, and the babies had been left near windows that did not have protective screens.

The patient's twin was asymptomatic. A peripheral blood smear showed no parasites; she had a leukocyte count of 11.6×10^9 per liter, a hemoglobin level of 115 grams per liter, and a hematocrit of 0.334 with a platelet count of 393×10^9 per liter.

The mother had a leukocyte count of 12.4×10^9 per liter, a hemoglobin level of 133 grams per liter, a hematocrit of 0.40, and a platelet count of 197×10^9 per liter. Her reticulocyte count was 0.02, and the peripheral blood smear did not reveal any malaria parasites. She was given a 14-day course of primaquine phosphate.

The results of serologic tests done at the Centers for Disease Control and Prevention are shown in Table 1.

Discussion

Congenital malaria is a well-described disorder with an occurrence as low as 0.3% in immune mothers to as high as 10% in nonimmune mothers.[3,8] The rarity of congenital transmission is attributed to the effectiveness of the placenta as a barrier to infected cells and to the pas-

TABLE 1.—*Indirect Fluorescent Antibody Titers to* Plasmodium vivax, Plasmodium falciparum, Plasmodium malariae, *and* Plasmodium ovale *Antigens in Serum Specimens From the Case Patient, the Mother, and the Other Twin*

Antibody Titers	*Patient*	*Mother*	*Other Twin*
IgG Titer			
P vivax	1:4,096	1:1,024	1:1,024
P falciparum	1:256	1:64	1:16
P malariae	1:256	ND	ND
P ovale	1:256	1:64	1:16
IgM Titer			
P vivax	1:1,024	1:16	ND
P falciparum	1:256	ND	ND
P malariae	1:64	ND	ND
P ovale	1:256	ND	ND

IgG = immunoglobulin G, IgM = immunoglobulin M, ND = none detected

sive transfer of maternal antibodies.[9] Postulated mechanisms for congenital transmission include maternal transfusion into the fetal circulation either at the time of delivery or during pregnancy, direct penetration through the chorionic villi, or through premature separation of the placenta.[9] Although various studies support each of these postulates,[3] transmission at parturition or during labor is thought to be the most likely mechanism.[2]

Immunoglobulin (Ig) M antibody synthesis can start during gestation, and the patient's high IgM titers represent an immunologic response by the infected twin. Immunoglobulin M antibodies may be present in patients with chronic malaria, and the mother's low titer probably indicates chronic low-grade infection.[10] The substantial titers to the heterologous antigens represent cross-reactivity and are not unusual. The IgG in the second twin is from passive acquisition from the mother.

Although the clinical presentation and serologic test results are consistent with either vector-transmitted or congenital malaria, this patient was most likely infected through perinatal transmission. She had never been in an endemic area, and although the *Anopheles* species vector is known to be present in Yuba City, autochthonous cases have not been reported to occur since 1974.[11]

The patient's fever, anorexia, lethargy, anemia, and splenomegaly are the classic presenting symptoms and signs of neonatal malaria. It takes a minimum of ten days for vector-borne malaria to incubate, and the mean presentation of congenital malaria is 5.5 weeks with a range of 0 to 60 weeks. Fever is invariably present, hepatosplenomegaly and anemia were noted in 84% to 93% of cases in a review,[2] and anorexia and lethargy have been described in several other reports. Most (69%) women whose infants have this disorder had fever during their pregnancy, and 38% had no detectable parasites on smear.[2] *Plasmodium vivax* is now the most commonly observed malarial species in California, reflecting immigration patterns. More than 90% of mothers of these infants whose immigration history is available have been in the United States less than 18 months.[2] The fact that the patient's mother was asymptomatic and without a previous history of malaria is not uncommon.

It is unclear why only one twin has been affected in the five reported cases. In one case, early placental separation and a difficult delivery were implicated as responsible for infection of the second twin.[5] In the only case of monozygotic twins reported, infection was documented only in the first twin and the mother; however, both twins were treated because of the possibility that the second twin had also been infected.[4] In our patient, in whom labor was premature, transmission most likely occurred at the time of delivery, especially because the second twin was the one affected.

The diagnosis of malaria in a neonate is frequently missed, it being usually mistaken for sepsis or infections in the TORCHS syndrome [*to*xoplasmosis, *r*ubella, *c*ytomegalovirus, *h*erpes, and *s*yphilis].[2] In a substantial number of patients, there is a long delay in diagnosis. The incidental finding of parasites by a laboratory technician can clinch the diagnosis, but in cases where there is a low parasite load, diagnosis can be delayed for weeks to months, resulting in substantial morbidity.

In patients who present with jaundice, anemia, fever, lethargy, and hepatosplenomegaly from birth to the first few months of life, malaria should be considered, especially when the infant's mother comes from an endemic area, even in the absence of recent travel. Serologic tests should be done when the peripheral smear is negative and there is a high index of suspicion or when it is not clear how malaria was acquired.

Response to therapy is usually good. In patients like ours, it is important to establish the mode of acquisition because vector-borne infection requires therapy for both the erythrocytic and exoerythrocytic stages, whereas congenital and transfusion-acquired malaria can be cured with treatment of only the erythrocytic stage. The mother received treatment for the exoerythrocytic stage, but the patient did not. The other twin did not require therapy.

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